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D E C I S I O N
of 27 March 2003

Case Number: T 0108/98 - 3.3.8

Application Number: 84305908.0

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Language of the proceedings: EN

Title of invention:
Molecularly cloned diagnostic product and method of use

Patentee:
GENENTECH, INC.

Opponent:
Dade Behring Marburg GmbH

Headword:
HSV glycoproteins/DADE BEHRING

Relevant legal provisions:
EPC Art. 54, 56, 87, 88, 89

Keyword:
"All claim requests - novelty (yes)"
"Inventive step (no)"

Decisions cited:
G 0009/92

Catchword:
-

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Case Number: T 0108/98 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 27 March 2003

Appellant: (Proprietor of the patent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 10 November 1997 concerning maintenance of European patent No. 0 139 416 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julia
C. Rennie-Smith

Summary of Facts and Submissions

I. An appeal was lodged by the patentee (appellant) against the interlocutory decision of the opposition division, whereby the European patent No. 0 139 416 with the title "Molecularly cloned diagnostic product and method of use" was maintained on the basis of the fifth auxiliary request filed at the oral proceedings before the opposition division. The patent claimed priority from three US applications filed on 30 August 1983, 31 October 1983 and 9 March 1984, respectively.

II. The patent had been opposed under Article 100(a) EPC for lack of novelty and inventive step. The opposition division decided that the main request (claims as granted) lacked novelty under Article 54(3) EPC. The first auxiliary request was found not to fulfill the requirements of Article 56 EPC. The second auxiliary request was refused under Article 123(3) EPC, whereas the third auxiliary request was refused under Article 84 EPC. The fourth auxiliary request was refused under Articles 123(2), 84 and 56 EPC and was considered not to meet the requirements of Rule 57a EPC.

III. Claim 1 as granted (**main request**) read as follows:

"1. A process which comprises producing in a recombinant, stable, mammalian, continuous cell line a gC or gD glycoprotein polypeptide of Herpes simplex virus type 1 or type 2 whereby the glycoprotein has exposed antigenic determinants capable of specifically binding complementary antibodies of Herpes simplex virus type 1 and/or type 2.".

Claims 2 and 3 were dependent on claim 1 and defined the association of the glycoprotein with the cell membrane. Claim 4 was directed to a process according to claim 1, wherein there was initially produced a truncated derivative of a membrane-bound gC or gD glycoprotein polypeptide of Herpes simplex virus type 1 or type 2 devoid of membrane-binding domain, whereby the derivative polypeptide was free of said membrane and had said exposed antigenic determinants. Claims 5 to 14 were dependent claims directed to further embodiments of the process of claims 1 to 4. Independent claim 15 was directed to a diagnostic test kit comprising the truncated, membrane-free polypeptide as obtainable by the process according to claim 4, claims 16 to 24 defining further embodiments thereof. Independent claims 25 and 29 were concerned with different methods of detection using said truncated, membrane-free polypeptide, claims 26 to 28 and claims 30 to 31 defining further embodiments thereof, respectively.

IV. The **fifth auxiliary request** accepted by the opposition division was concerned only and exclusively with subject-matter related to Herpes simplex virus type 2 glycoprotein C (gC-2).

V. With the statement of grounds of appeal on 28 March 1998, the appellant filed a second, fourth and fifth auxiliary requests. A first and a third auxiliary requests were filed on 25 February 2003 and on 21 October 2002, respectively. The fifth auxiliary request was the one accepted by the opposition division (cf Section IV *supra*), whereas all other auxiliary

requests corresponded to the ones treated during the opposition proceedings but with the correction of several omissions ("specifically" and "complementary") which were noted by the opposition division and in the decision under appeal.

VI. Independent claim 1 of the **first auxiliary request** was concerned with subject-matter relating to Herpes simplex virus type 2 glycoprotein C (gC-2), whereas independent claim 2 read as follows:

"2. A process which comprises producing in a recombinant, stable, mammalian, continuous cell line a gC or gD glycoprotein polypeptide of Herpes simplex virus type 1 or type 2, wherein there is initially produced a polypeptide devoid of membrane-binding domain, whereby the derivative polypeptide is free of membrane and has exposed antigenic determinants, and is capable of specifically binding complementary antibodies of Herpes simplex virus type 1 and/or type 2."

VII. The **second auxiliary request** comprised the twenty-nine claims of the first auxiliary request, wherein, however, the process claims of the first auxiliary request had been changed to claims directed to the use of the corresponding polypeptides in a diagnostic assay.

VIII. Independent claim 1 of the **third auxiliary request** read as follows:

"1. A process which comprises producing in a recombinant, stable, mammalian, continuous cell line a gC or gD glycoprotein polypeptide of Herpes simplex

virus type 1 or type 2 whereby the polypeptide is a type-specific fraction of the glycoprotein having exposed antigenic determinants capable of specifically binding complementary antibodies of Herpes simplex virus type 1 or type 2.".

Claim 4 was directed to the process of claim 1, wherein there was initially produced a truncated derivative of a membrane-bound gC or gD glycoprotein polypeptide of Herpes simplex virus type 1 or type 2 devoid of membrane-binding domain, whereby the derivative polypeptide was free of said membrane and had said exposed antigenic determinants.

IX. Claims 1 and 2 of the **fourth auxiliary request** were exclusively concerned with processes relating to Herpes simplex virus type 2 glycoprotein C (gC-2), whereas independent claim 3 read as follows:

"3. A process which comprises producing in a recombinant, stable, mammalian, continuous cell line a type-specific fragment of gC glycoprotein polypeptide of Herpes simplex virus type 1 or type 2 whereby the glycoprotein has exposed antigenic determinants capable of specifically binding complementary antibodies of Herpes simplex virus type 1 or type 2, respectively, and thereby capable of distinguishing between HSV-1 and HSV-2.".

Claim 7 related to a process according to any one of claims 1 to 4, wherein there was initially produced a truncated derivative of a membrane-bound gC glycoprotein polypeptide devoid of membrane-binding domain, whereby the derivative polypeptide was free of said membrane and had said exposed antigenic

determinants.

X. All the remaining claims of the first, second, third, fourth and fifth auxiliary requests essentially corresponded to the ones of the main request but referring to the specific glycoprotein polypeptides as defined above.

XI. The Board issued a communication pursuant to Article 11(2) of the Rules of Procedure of the Boards of Appeal outlining the points to be discussed. In particular, it was indicated that documents published after the first and second priority dates but earlier than the third priority date were relevant for assessing the inventive step of subject-matter not entitled to said priorities. With reference to decision G 9/92 (OJ EPO 1994, 875), the parties were reminded that neither the Board of Appeal nor the opponent could challenge the maintenance of the patent as amended in accordance with the interlocutory decision, as no appeal had been filed by the opposing party.

XII. Oral proceedings were held on 27 March 2003. As announced in its letter dated 25 February 2003, the appellant did not attend the oral proceedings. For reasons of procedural economy, and to give the absent appellant the benefit of any available doubt, the Board postponed discussions of issues arising under Articles 123 and 84 EPC until after discussion of issues of novelty and inventive step on subject-matter common to all requests.

XIII. The documents referred to in the present decision are the following:

D1a: EP-A-0 100 521 published on 15 February 1984 (filing date 27 July 1983);

D2: R.J. Watson et al., Science, 22 October 1982, Vol. 218, pages 381 to 384;

D2a: J.H. Weis et al., Nature, 3 March 1983, Vol. 302, pages 72 to 74;

D3: R.J. Frink et al., J. Virol., February 1983, Vol. 45(2), pages 634 to 647;

D6: J.K. Rose and J.E. Bergmann, Cell, October 1982, Vol. 30, pages 753 to 762;

D7: E. Amann et al., Gene, 1984, Vol. 32, pages 203 to 215;

D12: B. Norrild and B. Pedersen, J. Virol., August 1982, Vol. 43(2), pages 395 to 402;

D14: P.W. Berman et al., Science, 4 November 1983, Vol. 222, pages 524 to 527;

D16: US 4 399 216;

D17: M. Zoler and T. Wilson, Bio/Technology, April 1983, pages 146 to 147;

D31: N. Sarver et al., Mol. Cell. Biol., June 1981, Vol. 1(6), pages 486 to 496;

D32: J.T. Elder et al., Ann. Rev. Genet., 1981, Vol. 15, pages 295 to 340;

A1: A.D. Levinson, Methods in Enzymology, 1990, Vol. 185, pages 485 to 579.

XIV. The appellant's submissions in writing insofar as they are relevant to the present decision may be summarized as follows:

Article 54 EPC (Novelty)

Document D1a was concerned with the preparation of herpes simplex virus (HSV) antigens suitable for diagnostic and therapeutic uses and it was exemplified by cloning a genome section of HSV-1 corresponding to the gC glycoprotein (gC-1). The document referred, in general, to the expression of gC-1 in prokaryotic and eukaryotic host cells (cf end of Sections 3 and 5 and claim 7) but there was, however, no disclosure of any actual expression. In view of the important technical problems and difficulties found in expressing the gC-1 in prokaryotic host cells (cf document D7 and Exhibit 1, enclosed to the patentee's letter of 23 May 1994), the skilled person would not have contemplated the expression in eukaryotic host cells.

Documents D31 and D32, cited in document D1a, disclosed expression vectors for mammalian cells but there was no reference to the expression of any glycoprotein, let alone of any HSV glycoprotein. Document D31 disclosed minimal levels of expression using the BPV vector and thus, it would not have encouraged to use this BPV system for practical purposes such as the production of vaccines or diagnostic products. Moreover, the disclosed BPV vector did not provide a regulatory element to drive the transcription of the inserted gene but it used the one from the inserted gene. However,

the isolation of a suitable HSV regulatory transcription element was not straightforward. In any case, even as late as in 1990 (cf document A1), neither the BPV nor the SV40 eukaryotic expression systems were considered to produce stable transformed cell lines in a reliable manner.

Thus, the claimed subject-matter was novel over document D1a.

Article 56 EPC (Inventive step)

Document D3 was concerned with gC-1, however, it did not disclose the expression of gC-1 in host cells but only the in vitro translation of gC-1 mRNA in a rabbit reticulocyte system. It was neither obvious nor reasonable to expect the skilled person to go from an in vitro expression system to the recombinant, stable, mammalian, continuous cell lines of document D16. In fact, document D16 was a general disclosure of co-transformation for inserting DNA into eukaryotic mammalian cell lines but it was completely silent on HSV glycoproteins, let alone on gC-1 or on its possible use for diagnostic. In view of the additional technical problems and uncertainties (purification, toxicity, etc...), there was no reason to use the expression system of document D16 instead of other well-known and more established expression systems, such as E. coli, yeast or fungi. In particular, the toxic effects found in expressing HSV glycoproteins in E. coli were expected to be greater and more adverse for the amplification systems of document D16. Moreover, there was no indication in document D3 that the resulting gC-1 glycoprotein had the appropriate quality and immunoreactivity for its use in diagnostic assays. The

strong immunogenicity and better diagnostic properties resulting from the expression in the system of the contested patent were completely unexpected.

The identification of the glycoprotein transmembrane regions in documents D2 (gD-1) and D3 (gC-1) was only putative. Document D2a disclosed the expression of a fusion (truncated) gD-1 protein in a prokaryotic host cell but not the expression of a truncated gD-1 protein alone. The expression of a truncated membrane-devoid derivative was expected to interfere in the production of the normal HSV glycoprotein structure, such as the one of the gD trimer, altering thus the antigenic properties. In view of the problems and difficulties outlined in document D17 (presence of non-native structure, problems in obtaining polyvalent complexes for immunogenicity, presence of multiple hydrophobic regions, etc...), the production of a membrane-devoid derivative was not straightforward and obvious. Moreover, there was no reason to use the expression system of document D16, concerned with the expression of unaltered genes, instead of other more established and well-known expression systems. Document D6, disclosing the expression of a membrane-devoid derivative of a totally different virus (vesicular stomatitis virus) in mammalian cells, showed the problems encountered using such a system (no secretion or abnormally slow secretion of recombinant product, significant lower expression, etc...) and one of the exemplified host cells (COS cells with SV40-derived vector) was not a stable and continuous cell line in the sense of the contested patent.

Document D12 referred to gC-1 and gC-2 as being type-specific glycoproteins. However, the patent-

in-suit provided for the first time a rational basis for designing gC fragments with type-common and/or type-specific epitopes, allowing thus the diagnostic of sub-clinical HSV-2 infections which had been underdiagnosed with the available methods.

Thus, the claimed subject-matter was inventive over the cited prior art.

XV. The respondent's submissions in writing and during the oral proceedings insofar as they are relevant to the present decision may be summarized as follows:

Article 54 EPC (Novelty)

Document D1a, which was prior art under Article 54(2) EPC, referred to the expression of gC-1 and its use for vaccine and diagnostic purposes, the nucleotide and amino acid sequences of the gC-1 glycoprotein being known in the art (cf document D3). Document D1a exemplified the expression of gC-1 in a prokaryotic host cell. However, there was an explicit teaching for other host cells, such as general eukaryotic host cells and animal cell cultures, and reference was made to several expression vectors for mammalian cells known in the art, such as inter alia those of documents D31 and D32. Document D31 disclosed the BPV expression system with recombinant, stable, mammalian, continuous cell lines expressing significant levels of a recombinant product. The provision of suitable regulatory elements for the expression of genes inserted in this BPV system was within the normal abilities and the common general knowledge of the skilled person. Document D32, concerned with the SV40 eukaryotic expression system, represented a similar

disclosure. As the technical difficulties and problems found in the expression of HSV glycoproteins in prokaryotic hosts were known to the skilled person (cf document D7 and Exhibit 1), the production of these glycoproteins using their "natural" eukaryotic (mammalian) host cells, as indicated in document D1a, would have been contemplated by the skilled person.

Thus, the claimed subject-matter was not novel over the disclosure of document D1a.

Article 56 EPC (Inventive step)

Document D3 disclosed the nucleotide and amino acid sequences of gC-1 which was identified as a convenient type-specific marker. Mammalian expression systems were well-known in the prior art (cf document A1) and they were the expression system of choice for glycoproteins such as gC-1. In particular, document D16 referred to the advantages of mammalian expression systems with explicit mention of viral antigens and glycoproteins, and to the specific system used in the contested patent, namely the co-selection with the marker dihydrofolate dehydrogenase (DHFR).

Documents D2, D2a (gD-1) and D3 (gC-1) showed that these HSV glycoproteins were membrane-bound. In view of the known advantageous expression of truncated viral glycoproteins (production of truncated viral glycoproteins with viral antigenic determinants, cf documents D17 and D6), it would have been obvious to express these truncated glycoproteins using their normal host cells, ie using a well-known and available mammalian expression system (cf documents D16 and A1). Moreover, their use in HSV diagnostic assays or test

kits was also obvious and it did not require any special inventive contribution. In this respect, the claims of the contested patent did not require the HSV glycoproteins to be immunogenically stronger or to have better diagnostic properties. The presence of type-specific gC-1 epitopes was already known from D12 and it was obvious and easy for the skilled person to find type-specific fragments of a known glycoprotein.

Moreover, it was submitted that the subject-matter concerned with the gC glycoprotein and in particular with the gC-1, was obvious in the light of document D1a combined with document D14. Furthermore, documents D17 and D12 with the common general knowledge rendered the subject matter relating to truncated gC-1 and/or to type-specific gC-1 obvious.

Thus, the claimed subject-matter was not inventive in the light of the cited prior art.

XVI. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained as granted (main request) or on the basis of first auxiliary request filed on 25 February 2003, or second, fourth auxiliary requests filed on 20 March 1998 or the third auxiliary request filed on 21 October 2002.

The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

Procedural matters

1. Common to all claim requests on file are embodiments relating to the gC glycoprotein of HSV-1 (gC-1) and/or to its truncated derivative devoid of a membrane-binding domain. In view of this, leaving aside the issue of the compliance of the requests with the formal requirements of the Articles 84 and/or 123(2), (3) EPC, the Board finds it expedient to examine the said subject-matter as to its substance.

Articles 87 to 89 (Entitlement to priority rights)

2. The patent-in-suit claims three different priorities, namely US 527916 (30 August 1983), US 547552 (31 October 1983) and US 587763 (9 March 1984). The opposition division found that, while the embodiments relating to the gD glycoprotein were entitled to the first and/or second priority date, those relating to the gC glycoprotein enjoyed only the third priority. As indicated also in the minutes of the oral proceedings before the opposition division (cf page 1, 7th and 8th paragraphs) both parties agreed with this finding. Nor has this been disputed on appeal. The Board agrees with it.

Articles 54 EPC (Novelty)

3. In view of the finding on priority, document D1a, which was published on 15 February 1984, constitutes prior art under Article 54(2) EPC for the embodiments relating to gC-1.

4. According to the established jurisprudence of the Boards of Appeal, an invention lacks novelty over the prior art if its subject-matter is **clearly and directly** derivable from said prior art with all its technical

features. Moreover, this prior art must be enabling in the sense that it must provide the technical means to achieve said subject-matter in a straightforward manner (cf Case Law of the Boards Appeal, 4th edition 2001, page 54, point 2 and page 66, point 2.12).

5. Document D1a discloses the isolation of a genomic DNA fragment of the Herpes simplex virus type 1 encoding the full-length glycoprotein gC (gC-1) (cf page 3, line 1 to page 4, line 6). The document refers to the expression of this HSV-1 DNA fragment in prokaryotic cells, in particular Escherichia coli, as well as in eukaryotic cells, with reference to suitable plasmids and expression vectors (cf page 4, line 8 to page 5, line 3). In this respect, both yeast and animal cell cultures are explicitly mentioned with reference to their advantageous use for glycosylation purposes (cf page 7, lines 21 to 23 and claim 7). All the plasmids and expressions vectors indicated for expression in eukaryotic cells are specific for mammalian host cells, such as the Bovine Papilloma Virus (BPV) DNA, the SV40 or the chimeric pSG plasmids, which are cited by cross-reference to documents D31 and D32 (cf page 4, line 34 to page 5, line 3). Document D1a further suggests the production of gC-1 fragments with antigenic determinants (cf page 6, lines 9 to 16) as well as the use of the gC-1 products for general diagnostic purposes such as the detection of antibodies against Herpes simplex virus or the production of antisera which can be used to detect HSV (cf page 7, lines 29 to 34 and claim 10).

6. The Board understands document D1a as disclosing **clearly and directly** a process which comprises producing in recombinant, mammalian cell lines a gC-1

glycoprotein and general fragments thereof with exposed determinants capable of specifically binding complementary antibodies of HSV-1. Moreover, this document provides the technical means (gC-1 DNA, suitable expression vectors, etc...) for carrying out said process in a straightforward manner. Document D1a **explicitly** discloses all the features present in the cell lines of the patent-in-suit except for the ones requiring these recombinant, mammalian cell lines to be **stable** and **continuous**. The question arises, however, as to whether these two additional features are **implicitly** disclosed in document D1a. In particular, it has been argued that using the eukaryotic expression vectors cited in document D1a, and more particularly the ones of documents D31 or D32, cell lines with all the required features, ie recombinant, **stable**, mammalian, **continuous** cell lines, would be directly achieved.

7. Document D31 discloses the transformation of mouse C127-I cells by recombinant BPV DNA comprising the heterologous rat preproinsulin gene 1. The recombinant sequences remain in a free, non-integrated episomal form and the transformed cell colonies are isolated and established as cell lines (cf page 490, left-hand column, first full paragraph), ie as recombinant, **stable**, mammalian, **continuous** cell lines. The DNA inserted into the BPV vector contains the coding sequence of the gene, its intervening sequence and the regulatory signals at the 5' and 3' termini (cf page 487, right-hand column, fourth paragraph), ie all of the regulatory signals (putative promoter, polyadenylation site, and intervening sequences) necessary for faithful transcription (cf page 494, right-hand column, third full paragraph). However, viral promoter and termination signals are also present

in the BPV vector, and even if they do not appear to regulate the transcription of the heterologous gene, a detailed analysis of the 5' end is said to be in progress (cf page 493, left-hand column, second full paragraph and page 495, left-hand column, first full paragraph).

8. Document D1a refers to a digestion of the 5' terminus of the isolated genomic DNA fragment and ligation with suitable promoters (cf page 5, line 30 to page 6, line 7). Document D1a does not disclose any nucleotide sequence but refers to a document by Fink et al., J. Virol., **in press** which is likely to be document D3 (cf page 5, lines 31 to 32) and which identifies the sequences of the gC-1 promoter and the 3' termination signals. Thus, the skilled person when trying to put into practice the teachings of document D1a using the BPV system of document D31 would be faced with several possible choices, namely to use (i) the BPV viral regulatory signals, (ii) the ones of the rat preproinsulin gene 1, (iii) the regulatory signals of gC-1 without the BPV regulatory signals or (iv) with these BPV regulatory signals. The choice of any one of these possible alternatives and the result achieved thereby (vector and/or host cell stability, presence or absence of correct transcription, etc...) is, in the Board's view, far from being clear and straightforward.

9. Document D32, which is a general review of the Simian Virus 40 as an eukaryotic cloning vehicle, refers to all possible types of SV40 vectors, including the ones using a lytic cell cycle which are quite different from the stable and continuous cell lines of the patent-in-suit. Even for those SV40 vectors which do not use this lytic cycle "... *one may not expect stable*

extrachromosomal replication over many cell generations in culture ..." (cf page 317, second full paragraph) unless the foreign DNA fragment is topologically linked to selectable genes (cf paragraph bridging pages 321 to page 322). Therefore, not all of the SV40 vectors disclosed in document D32 result in the production of recombinant, **stable**, mammalian, **continuous** cell lines and it requires to choose a specific type of SV40 vectors among all other possible ones for achieving all these features. Thus, not all of the features characterizing the cell lines of the patent-in-suit are clearly and directly derivable from this document.

10. The Board concludes that the embodiments of the patent-in-suit relating to a process of producing in a recombinant, stable, mammalian, continuous cell line a gC-1 glycoprotein is not (explicitly or implicitly) **clearly and directly** derivable from document D1a. None of the other embodiments of the patent-in-suit has been objected under Article 54 EPC and, in view of the cited prior art, the Board does not see any reason to question their novelty of its motion. Thus, the novelty of the claimed subject-matter of all requests is acknowledged.

Article 56 EPC (Inventive step)

11. The closest prior art for the subject-matter relating to the gC-1 glycoprotein is considered to be document D1a. As stated in item 5 above, this document refers to gC-1 and general fragments thereof with antigenic determinants as well as to the use of these gC-1 products for general diagnostic purposes. Moreover, document D1a further points to the desirable glycosylation obtained by expressing these gC-1

products in eukaryotic host cells.

12. Starting from this closest prior art, the objective technical problem underlying the contested patent must be seen in the provision of a suitable eukaryotic expression system for the production of the gC-1 glycoprotein and suitable fragments thereof. The patent-in-suit solves this technical problem by the provision of recombinant, stable, mammalian, continuous cell lines producing the gC-1 glycoprotein and fragments thereof such as a truncated (type-specific) gC-1 fragments devoid of the membrane-binding domain.

13. The teachings of document D1a are said to be generally applicable to other HSV glycoproteins such as gA, gB, gD and gE (cf page 2, lines 16 to 19 and page 7, lines 1 to 3). In the same manner, expression systems used for the production of one or some of these glycoproteins would be expected to be applicable to the known gC-1 glycoprotein too. In particular, document D14, which corresponds to the publication of the contents of the first two priority documents of the patent-in-suit, discloses the production of the gD-1 glycoprotein using the recombinant, **stable**, mammalian, **continuous** cell lines of the patent-in-suit. This document emphasizes the advantages of the disclosed expression system over other known expression systems, particularly the possibility of developing useful diagnostic reagents, and it states that the described strategy "... *could be applied to any situation where the expression of a membrane protein is desired.*" (cf page 527, left-hand column, last sentence). In view of the known general advantages of eukaryotic expression systems (cf column 1, lines 29 to 52 of the patent-in-suit for the purpose of acknowledging the prior art,

and document D16, column 2), it would have been obvious for the skilled person faced with the stated problem to use these systems for expressing the gC-1 glycoprotein or fragments thereof. In the light of the successful production of the gD-1 glycoprotein, the skilled person would have had more than a reasonable expectation of success when using the particular expression system of document D14 for the gC-1 glycoprotein of document D1a and fragments thereof.

14. In fact, document D1a refers to gC-1 fragments comprising antigenic determinants relevant for diagnostic purposes (cf item 5 *supra*). For membrane-bound glycoproteins, these antigenic determinants are expected to be found particularly in the extracellular domain and the advantages of producing immunologically or antigenically active truncated glycoprotein derivatives devoid of the membrane-binding domain were well-known in the prior art as shown by document D17 (easy and quick purification). The membrane binding-domain of the gC-1 glycoprotein had already been identified in the art (cf document D3, page 642, Figure 5). Thus, the Board considers that the production of a truncated gC-1 glycoprotein devoid of membrane-binding domain using the expression system of document D14 (cf item 13 *supra*) would have been obvious to the skilled person in the light of the common general knowledge.

15. The appellant has referred to several technical problems and uncertainties that would have jeopardized any reasonable expectation of success (cf Section XIV *supra*). In particular, it has been alleged that the deletion of the membrane-binding domain of the gC-1 glycoprotein would have been expected to interfere with

the normal production of the native gC-1 glycoprotein structure and thus, resulting in a truncated gC-1 glycoprotein with altered immunogenic properties. However, in view of the prior art, which shows a strong resilience of the structure of these HSV glycoproteins, the Board cannot follow this line of argumentation.

16. Document D3 shows that the gC-1 glycoprotein produced by an in vitro expression system and thus, in absence of other HSV-1 proteins and of any normal cellular (membrane) component, could nevertheless be purified by immune precipitation with a polyvalent antibody to HSV-1 envelope protein (cf page 636, left-hand column, third full paragraph). In a similar manner, document D14 shows that the gD-1 glycoprotein produced by mammalian cell lines as in the patent-in-suit "... *has a number of antigenic determinants in common with the native HSV-1 virus and that the structure of these determinants* ***is not dependent on interactions with other HSV-1 proteins*** *..."* (cf page 526, middle column, highlighted in bold type by the Board). More relevant is the disclosure of document D2a which shows that a fusion protein comprising a completely unrelated protein and a truncated gD-1 glycoprotein devoid of the membrane-binding domain (truncated gD-â-galactosidase) not only is immunologically active after undergoing harsh production and purification conditions but it is also able to elicit antibodies that immunoprecipitate gD-1 from cells infected with HSV-1 and to neutralize HSV-1 infectivity *in vitro*.

17. It is noted that the claimed processes do not require any particular yield, binding affinity or specificity except for the general requirement that the exposed antigenic determinants of the gC-1 glycoprotein must be

capable of specifically binding complementary antibodies of Herpes simplex virus type 1 and/or type 2. None of the alleged factors or difficulties would have lowered the expectations of the skilled person of achieving such a general result.

18. Thus, the Board considers that the production of gC-1 and fragments thereof, in particular of a truncated gC-1 glycoprotein devoid of a membrane-binding domain, using the expression system of document D14 (cf item 13 *supra*) would be obvious to the skilled person and that, in the light of the prior art, said skilled person would have a reasonable expectation of success.

19. Furthermore, in view that (**i**) there were well-known techniques available to the skilled person for easily determining the type-specificity of a gC-1 fragment (standard serological assays comparing cross-reactivity with antisera raised to HSV-1 and/or to HSV 2, immunological tests such as (radio)immunoprecipitation, immunoblotting, virus neutralization, etc...) (cf columns 1 to 4 of the patent-in-suit acknowledging the prior art), (**ii**) that the cited prior art clearly identifies the antigenic determinants of the gC-1 glycoprotein as being predominantly type-specific (cf column 2, lines 19 to 24 and column 3, lines 37 to 44 of the patent-in-suit; document D12, page 395, left-hand column), and (**iii**) that the importance of the gC-1 glycoprotein as a type-specific gC-1 marker had already been clearly identified in the prior art (cf document D3, page 646, right-hand column, full paragraph), the additional features "type-specific" and "capable of distinguishing between HSV-1 and HSV-2" on their own cannot contribute to any possible inventive step in the subject-matter of the claims.

20. Thus, as all requests on file comprise subject-matter relating to the gC-1 glycoprotein and/or a (type-specific) truncated gC-1 devoid of membrane-binding domain, which, as shown in items 11 to 19 above, does not fulfill the conditions of Article 56 EPC, the Board concludes that none of these requests meets the requirements of the EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani